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Research Report

Localizing the distributed language network responsible for the N400 measured by MEG during auditory sentence processing

Burkhard Maess^{a,*}, Christoph S. Herrmann^b, Anja Hahne^a,
Akinori Nakamura^{c,a}, Angela D. Friederici^a

^aMax Planck Institute for Human Cognitive and Brain Sciences, PO box 500355; 04303 Leipzig, Germany

^bInstitute of Psychology, Otto-von-Guericke-Universität Magdeburg, Germany

^cDepartment of Brain Science and Molecular Imaging, National Institute for Longevity Sciences, National Center for Geriatrics and Gerontology, Aichi, Japan

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the magnetic equivalent N400m

ROI, region of interest

ABSTRACT

We studied auditory sentence comprehension using magnetoencephalography while subjects listened to sentences whose correctness they had to judge subsequently. The localization and the time course of brain electrical activity during processing of correct and semantically incorrect sentences were estimated by computing a brain surface current density within a cortical layer for both conditions. Finally, a region of interest (ROI) analysis was conducted to determine the time course of specific locations. A magnetic N400 was present in six spatially different ROIs. Semantic anomalies caused an exclusive involvement of the ventral portion of the left inferior frontal gyrus (BA 47) and left pars triangularis (BA 45). The anterior parts of the superior (BA 22) and inferior (BA 20/21) temporal gyri bilaterally were activated by both conditions. The activation for the correct condition, however, peaked earlier in both left temporal regions (approximately 32 ms). In general, activation due to semantic violations was more pronounced, started later, and lasted longer as compared to correct sentences. The findings reveal a clear left-hemispheric dominance during language processing indicated firstly by the mere number of activated regions (four in the left vs. two in the right hemisphere) and secondly by the observed specificity of the left inferior frontal ROIs to semantic violations. The temporal advantage observed for the correct condition in the left temporal regions is supporting the notion that the established context eases the processing of the final word. Semantically incorrect words that do not fit into the context result in longer integration times.

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1. Introduction

Sentence comprehension requires the identification of the words' meaning as well as their grammatical relation. When

processing sentences, each incoming word has to be integrated into the prior context. Successful integration is achieved when the new input matches the syntactic as well as the semantic constraints build up by the context. A mismatch

* Corresponding author. Fax: +49 3425 887511.

E-mail address: maess@cbs.mpg.de (B. Maess).

between the contextual constraints and the incoming word, be it a semantic mismatch or a syntactic mismatch, leads to increased processing time (Stanovich and West, 1983; Zwitserlood, 1989).

Brain responses to spoken language as measured by electroencephalography (EEG) or magnetoencephalography (MEG) differ as a function of the mismatch type: a mismatch with respect to syntactic aspects (word category) leads to an early left anterior negativity (ELAN) followed by a late positivity (P600) whereas a semantic mismatch leads to a negativity around 400 ms (N400) (Hahne and Friederici, 2002). The ELAN is probably related to the detection of the syntactic mismatch whereas the later P600 reflects processes of reanalysis (Friederici, 1995, 2004; Münte et al., 1998). The N400 in response to semantic violations has been observed for spoken (Holcomb and Neville, 1991), as well as for written language (Kutas and Hillyard, 1980). It has been observed as a function of a word's semantic unexpectedness at the sentence (Kutas and Hillyard, 1980) and at discourse level (van Berkum et al., 1999), as well as when words are presented as pairs (van Petten, 1995), for a review see Kutas and Federmeier (2000) and Kutas and Van Petten (1994). The N400 is taken to reflect post-lexical semantic integration processes (Chwilla et al., 1995).

The neural basis of the N400 is a matter of current research. It has been proposed that the N400 arises from a number of different generators (Halgren et al., 1994a,b; Nobre and McCarthy, 1995; Meyer et al., 2005). Based on data from deep intracranial recordings during word reading, medial temporal structures close to the hippocampus and the amygdala have been suggested as possible locations for the N400 generators (Halgren et al., 1994a). Intracranial recordings from the rhinal cortex and the hippocampus proper suggest that the rhinal cortex is the relevant structure in the medial temporal lobe supporting processes of semantic integration as reflected by the N400 (Meyer et al., 2005). Data from more superficial intracranial recordings, however, suggest that the superior temporal sulcus and additional frontal areas are involved in the generation of the N400 (Halgren et al., 1994a,b). A spatially more global approach is the use of whole-head MEG recording (Marinkovic et al., 2003; Halgren et al., 2002; Helenius et al., 1998, 2002) to identify the generators of the N400. Several studies reported structures in the "immediate vicinity of the auditory cortex" to be implicated most consistently with the processing of semantically anomalous sentences using equivalent current dipole analysis (Helenius et al., 2002; Mäkelä et al., 2001; Halgren et al., 2002).

Recently, distributed source modeling has been applied to MEG data to specify the areas involved in the generation of the N400 during reading semantically incongruent sentences (Halgren et al., 2002). The analysis identified quite a number of structures involved in processes reflected by the N400, namely, the left planum temporale, the left superior and inferior temporal sulci, the left temporal pole and the rhinal sulcus, the left insula, and the collateral sulcus at the occipitotemporal junction, the left prefrontal cortex (gyrus rectus, inferior frontal gyrus, dorsolateral prefrontal, and frontopolar cortices), as well as the right

orbital cortex. These regions were taken to constitute the neural network held responsible for contextual semantic processing. Although the authors provide a description of the time course of activation of the different areas, with the temporal areas preceding the frontal areas, they do not offer a functional specification of the different areas. In addition, these MEG data are not entirely consistent with recent fMRI findings for semantically anomalous sentences, which indicate a more bilaterally distributed, though left dominant network (Friederici et al., 2003; Kuperberg et al., 2000; Newman et al., 2001). Marinkovic et al. (2003) using another whole-head MEG data set determined a semantic processing network consisting of lateral frontotemporal cortices. Stronger left lateralization was observed when sentences were presented visually than when presented auditorily.

Two studies tried to integrate ERP and fMRI recordings using the same stimulus material. One study applied ERPs and fMRI during sentence reading using the same pragmatic anomalies (Kuperberg et al., 2003). An N400 effect was found in the electrophysiological measures. The fMRI results revealed increased activation in the left middle and inferior frontal cortex [Brodmann's areas (BA) 46, BA 44/45, and BA 47] and in the left superior temporal gyrus (BA 22). These brain areas are considered to be involved in the generation of the N400. Another fMRI study investigated the processing of semantic anomalies in connected speech (Friederici et al., 2003) using the same sentence material as in a previous ERP study (Hahne and Friederici, 2002). This study identified a more bilaterally distributed temporofrontal network involving the left and right superior temporal gyrus, the insulae bilaterally, and the right inferior premotor cortex for the processing of semantically anomalous sentences that elicited the N400 effect. From the different studies, it appears that the core areas involved in semantic processes reflected by the N400 are the temporal cortex and portions of the frontal cortex in the left and the right hemisphere, but that the auditory N400 during listening to verbal material recruits the right hemisphere more than the visual N400 during reading.

The most important difference between the abovementioned N400 studies was probably the type of material that was used. When considering the sentence processing studies only, they either used a visual word-by-word presentation (e.g., a MEG study by Halgren et al., 2002), an auditory word-by-word presentation (e.g., a MEG study by Helenius et al., 2002), or auditory connected speech presentation (e.g., an fMRI study by Friederici et al., 2003). To investigate whether the different neuroanatomical activations are due to difference in stimulation or due to the different methods used, we performed a MEG study. Especially, we wanted to estimate the temporal activation pattern of brain regions activated by semantic processing of connected speech complementing recent fMRI studies which used the identical stimulus material (Friederici et al., 2003; Rüschemeyer et al., 2005). Distributed source analysis (referred to as brain surface current density, BSCD) was applied to deal with the problem of multiple sources, which are not point-like. Time courses of spatial ROIs were computed as mean currents across these regions.

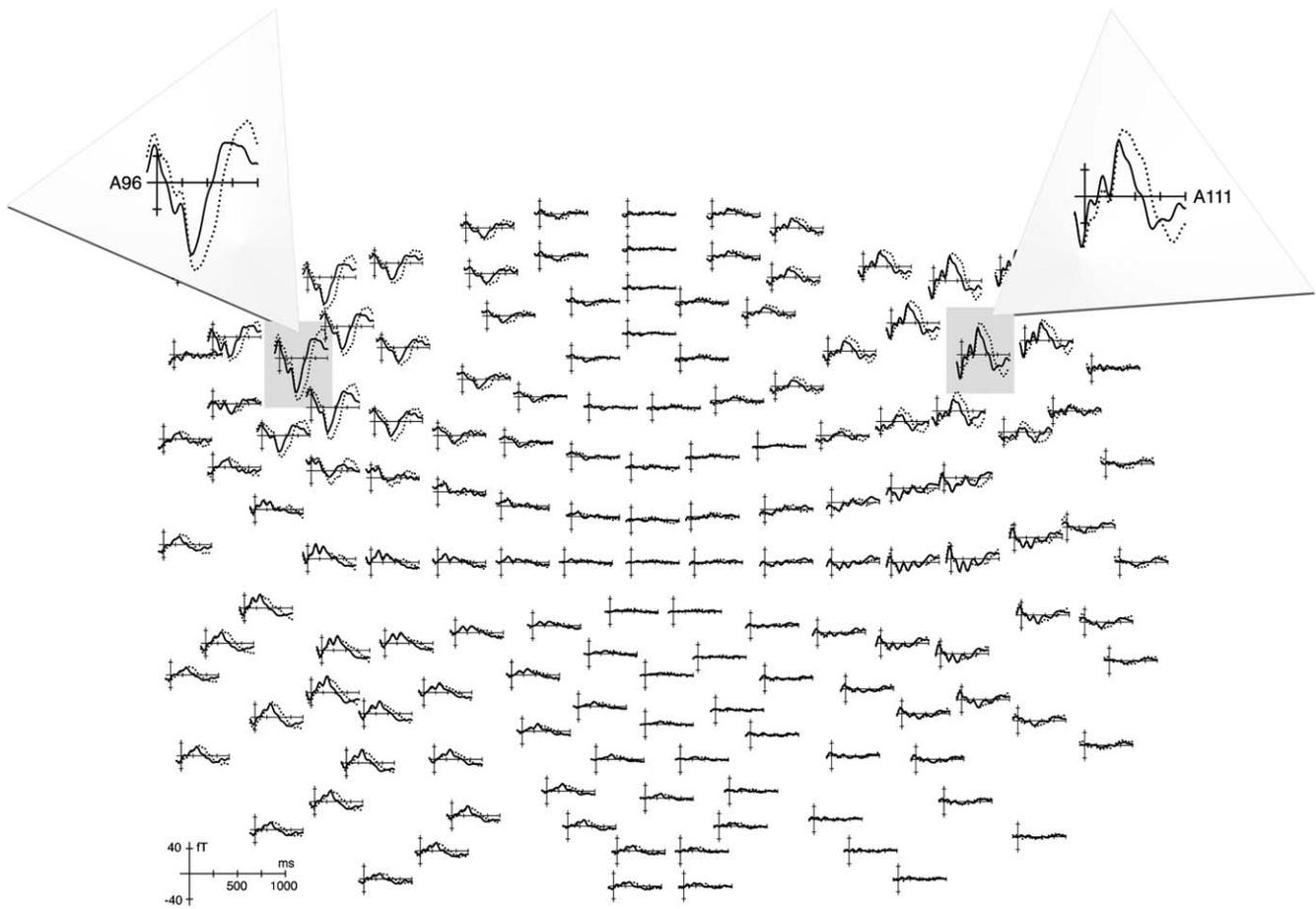


Fig. 1 – Signal traces for all 148 MEG channels comparing the evoked field responses for semantically incorrect (dotted) and correct (solid) sentence final words averaged over all subjects. Two signals (left: A96, right: A111) of frontal MEG channels are magnified.

Therefore, we derived the following hypotheses/questions for our study:

Hypothesis 1. We expected the abovementioned fronto-temporal network that was identified using fMRI (Friederici et al., 2003) to be active also in MEG during both the semantically incorrect as well as the correct condition when using the identical stimuli, task, and presentation modality. However, the activation should be stronger for the semantic violation, given the previous fMRI and EEG studies using the same material (Friederici et al., 2003; Hahne and Friederici, 2002).

Hypothesis 2. In addition, we expected the network to be lateralized to the left hemisphere due to the language specificity of the semantic violations. Furthermore, we also expected right hemisphere activity because of the auditory stimulation (Friederici et al., 2003).

Hypothesis 3. Additionally, we hypothesized that the regions are activated in a temporal–frontal sequence resulting in a systematic time lag of frontal cortex, which receives the auditory input later than the temporal cortex (Halgren et al., 2002).

Hypothesis 4. Finally, we expected the activation during the semantically incorrect condition to peak later or to last longer as compared to the correct condition, reflecting the additionally required time for integration (Zwitsersloot, 1989).

2. Results

Subjects performed well during the judgment task. On average, 94% of the answers were correct and in no condition performance was worse than 92%. The mean-evoked field response showed clear peaks as early as at about 300 ms for the correct condition and at about 340 ms for the incorrect condition (Fig. 1). The difference between conditions also starts at about 330 ms and had maxima around 500 ms. The strongest deflection appeared over frontal areas in both hemispheres. Central and occipital channels did not show strong evoked fields.

The results of the BSCD analysis revealed six regions of interest (ROIs) that showed pronounced activity in consequence of the semantically incorrect condition within the time interval from 300 to 550 ms (LIFG: the ventral portion of the left inferior frontal gyrus; LBroca: Broca's area in the left hemisphere; LSTG: the anterior part of the left superior

Table 1 – Locations (*x, y, z*) of the eight ROIs in Talairach coordinates

ROI	Brodmann	x (mm)	y (mm)	z (mm)
LBroca	45 (44)	-49	17	17
LIFG	47	-39	29	-6
LITG	20/21	-48	-5	-21
LSTG	22	-57	-12	-2
RBroca	45	49	31	8
RIFG	47	38	38	-5
RITG	20/21	51	-4	-19
RSTG	22	57	0	6

temporal gyrus; RSTG: the anterior part of the right superior temporal gyrus; LITG: left inferior temporal gyrus; RITG: right inferior temporal gyrus). If a region showed strong activation in one hemisphere, its homologue in the other hemisphere was also considered for analysis—even if showed weaker activity. This applied to the following regions: RBroca: Broca's area in the right hemisphere; RIFG: the ventral portion of the right inferior frontal gyrus. For Talairach coordinates of the centers of all ROIs, see Table 1. All eight ROIs with their respective time courses of activation in the two conditions are displayed in Fig. 2. Concerning the Brodmann areas corresponding to the two regions labeled as LBroca and RBroca: According to the cytoarchitectonic analysis provided by Amunts et al. (1999), our RBroca region is located in BA 45 (50%). Our LBroca seems to be located at the border between

both areas BA 45 (50%) and BA 44 (50%). Percentages given in the parentheses refer to number of cases in which Amunts et al. (1999) could cytoarchitectonically estimate cortex from this location as belonging to this specific Brodmann area. Although the center of our LBroca region seems to include BA 44 and BA 45 with same probability, we like to point out that LBroca appears to be the most superior edge and a local maximum of a BSCD activity pattern that connects LIFG and LBroca (see the red area between both regions in Fig. 2). Taking the connecting ridge into consideration supports the view that our LBroca region is best referred to as BA 45.

Within the first time window (300–400 ms), only the two left frontal regions (LIFG, LBroca) revealed a significant condition effect (cf. left panel in Table 2). During the later time window (450–550 ms), significant differences were found in six of the eight ROIs (cf. right panel of Table 2).

The tests for latency differences between ROIs revealed no significant differences when comparing within conditions. However, testing across conditions but within ROIs yielded a significantly later (about 32 ms) activation during the semantically incorrect condition in both temporal regions of the left hemisphere (LITG, LSTG).

3. Discussion

The present study used a whole-head MEG (148 channels) and applied a brain surface current density-based source

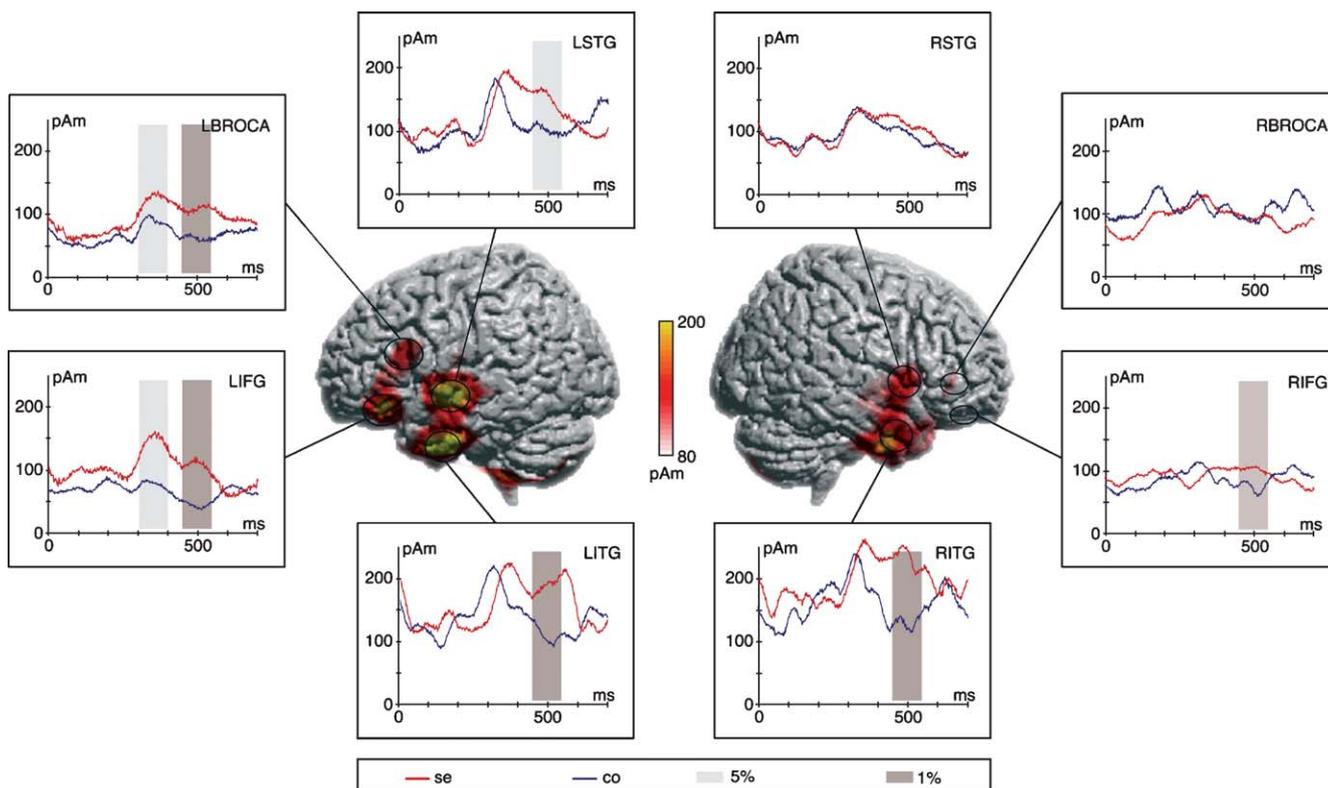


Fig. 2 – Views onto the left and right hemispheres displaying the mean current distribution of the semantically incorrect condition at a latency of 350 ms. The mean time courses for each of the specified regions of interest (ROI) and the two experimental conditions are displayed in boxes: red—semantically incorrect, blue—correct. The ROIs are visualized by black outlines. Gray bars indicate that the *t* test for this time interval yielded a significant difference between conditions ($P < 0.05$: light gray; $P < 0.01$: dark gray).

Table 2 – Mean values of semantic (se) violation and correct (co) condition as well as for the difference violation minus correct (se-co) computed for two time windows (300–400 and 450–550 ms) for each ROI separately

ROI	Mean, 300–400 ms			t test of se-co		Mean, 450–550 ms			t test of se-co	
	co [pAm]	se [pAm]	se-co [pAm]	P	t	co [pAm]	se [pAm]	se-co [pAm]	P	t
LBroca	88	124	36	0.021	2.54	62	109	47	0.002	3.58
LIFG	77	145	68	0.032	2.34	44	107	63	0.002	3.68
LITG	186	195	9			110	189	79	0.043	2.18
LSTG	148	173	25			102	152	50	0.003	3.46
RBroca	113	117	4			94	93	–1		
RIFG	98	97	1			75	102	27	0.036	2.28
RITG	206	236	30			131	232	101	0.002	3.60
RSTG	126	127	1			97	113	16		

Differences were tested for significance using a paired t-test.

localization¹ to identify the brain regions involved in processing semantic anomalies during auditory sentence comprehension. One major magnetic deflection was observed at frontal channels within a time window from 250 to 550 ms in both experimental conditions. The difference between the conditions started approximately at 350 ms and lasted also until 550 ms. This can be taken as the N400m, the magnetic counterpart to the negative potential evoked around 400 ms (N400).

3.1. Discussing Hypothesis 1

We found the expected frontotemporal network to be activated in both conditions (first part of Hypothesis 1). In addition to the previously identified regions, our study revealed inferior temporal regions to be involved. This is in line with the results of Marinkovic et al. (2003). Note that this is not in contrast to Rüschemeyer et al. (2005) because they did not record signals from these most inferior slices in their fMRI experiment. The frontotemporal network activated in our study partially overlaps with those regions identified by Friederici et al. (2003). The non-overlapping parts are presumably due to the fact that their study compared the semantically incorrect condition to a baseline while we contrasted them with the correct condition. Furthermore, we were able to demonstrate that activation during the later time interval was only due to semantic violations. This is in accordance with our expectation to find enhanced activity for the semantically incorrect condition (second part of Hypothesis 1). The observed activation pattern in the temporal regions in response to the semantic violation (N400 effect) is also in partial agreement with earlier MEG studies. Helenius et al. (1998) have observed the N400 activation during reading in the left temporal cortex (in 8 of 10 subjects) and in the right temporal cortex (in 5 of 10 subjects) using a whole-head MEG. These activations, however, were localized posterior in the STG. Halgren et al. (2002) revealed activation in Wernicke's area spreading to anterior

¹ Note that the locations found in this study do not only depend on the measured evoked fields, but also on the model used for the head (volume) and the possibly activated regions (sources). This is a general issue for all MEG localization procedures because wrong models could potentially be fitted to the measured data. In order to discuss the plausibility of our spatial estimates, we compare our solutions with current findings of e.g., corresponding fMRI studies.

temporal sites involving superior and inferior temporal sulci. The activation reported for these anterior temporal areas is in line with the predominant activation in the present study.

3.2. Discussing Hypothesis 2

In line with Hypothesis 2, we found significant differences between conditions in all of the ROIs in the left hemisphere but only in half of the ROIs in the right hemisphere. This is in agreement with our lateralization hypothesis as we found more active regions in the left hemisphere; specifically, the left frontal regions were exclusively activated during the processing of the semantically incorrect condition. On the other hand, our inferior temporal and inferior frontal regions revealed bilateral differences between conditions. This may be due to the fact that we used auditory sentence material. Marinkovic et al. (2003) compared auditory and visual presentation of words and found that auditory presentation resulted in more bilateral activations. The observed bilateral temporal activation in RITG/LITG has also been observed by Helenius et al. (1998). In contrast, Halgren et al. (2002), who only tested male participants, found a much clearer lateralization to the left hemisphere and discussed the possibility of gender being a relevant factor for this lateralization. This may also be an additional factor explaining the observed bilateral activity because we recorded male as well as female subjects.

3.3. Discussing Hypothesis 3

In contrast to Hypothesis 3, we were not able to find the expected temporal lag of frontal as compared to temporal brain regions. Such a temporal difference between ROIs was neither found for the semantically incorrect nor the correct condition. A reason for not finding a significant lag could be the expected size of the lag itself. An effect in the order of 20 ms might be just at the border of detectability because of the variance between subjects and the limited spatial resolution of the source localization method. The latter concern is especially important for comparisons between ROIs within the same condition.

3.4. Discussing Hypothesis 4

In line with Hypothesis 4, the tests for latency differences revealed that within the two left temporal regions the correct

condition peaked before the semantically incorrect condition. This latency difference was only present within the left hemisphere, which is further evidence for a language-specific lateralization (Hypothesis 2). Concerning the onset of neuronal activity, no significant differences were found between different regions within either the correct or the semantic violation condition. However, activity due to correct sentence endings started earlier in two left-hemispheric regions, namely, LSTG and LITG. D'Arcy et al. (2005) have recently reported similar latency differences of the N400 peak amplitude. That study was able to demonstrate that increased working memory load in a semantic N400 task resulted in delayed N400 amplitudes as compared to a lower working memory load. Halgren et al. (2002) also revealed N400 latency differences within a MEG study. Even though those authors did not analyze the latency of the magnetic N400 fields explicitly, their Fig. 1 displays about 50 ms of latency difference for the peak amplitude.

Such a latency difference indicates that some neural process probably requires more time in the semantically incorrect condition. Kutas and Federmeier (2000) have argued that one of the mental processes reflected by the N400 amplitude is search within the mental lexicon. This notion was brought up by studies of Bentin et al. (1985) and Holcomb (1993), who were presenting word pairs and demonstrated a reduced N400 amplitude if the first word primes the semantic context of the second (semantic priming effect). This reduced N400 amplitude was taken to indicate the faster search in long-term memory for the primed word. Further evidence for the search hypothesis stems from another study of Bentin (1987) using words and pseudowords. An increased N400 to pseudowords most probably results from a longer search within long-term memory because the whole mental lexicon needs to be searched before it is certain that the pseudoword is not a word. For words, however, the search is finished as soon as the item is found, which should be faster on average. In addition, Rugg (1990) and van Petten and Kutas (1990) have demonstrated that words that are frequently used within a language produce a reduced N400 amplitude compared to less common words which could be explained by better established memory traces in long-term memory resulting in quicker and more effortless search. Furthermore, in a behavioral experiment, Zwitserlood (1989) could demonstrate that a preceding context eases and accelerates the processing of the current word.

For the above reasons, our results are well in line with the notion of Kutas and Federmeier (2000) that the N400 amplitude is not only modulated by the semantic incongruency but by the time the neural processes require to integrate a word into the preceding context (which may fail in case of semantic violations).

3.5. Conclusion

The present results together with previous data indicate that the N400 effect reflecting the processing of semantically anomalous sentences is mainly based on activation in a temporofrontal network of both hemispheres with a clear dominance of the activation in the left hemisphere. The different regions of the cortical network are activated simul-

Table 3 – A complete set of all four sentences types used in the experiment

Correct	Die Melodie wurde gepfiffen. [The melody was whistled.]
Semantically incorrect	Der Mülleimer wurde gepfiffen. [The trash bin was whistled.]
Filler correct	Das Lied wurde beim Spaziergang gepfiffen. [The song was during the walk whistled.]
Filler incorrect	Das Kinderlied wurde beim gepfiffen. [The children's song was during the whistled.]

The same word is used in all four conditions at sentence final position. Different preceding contexts establish different experimental conditions. English translations retain German word order. Note that for the two relevant conditions (semantically incorrect and correct) also the penultimate word was identical.

taneously. Processing of the correct sentence final words might be easier and may therefore result in a temporal advantage (approximately 32 ms). The delayed activation of the semantic violation condition probably reflects higher processing demands while trying to integrate a non-fitting word into existing sentential context. Processing of semantically incorrect sentence final words results in stronger activation and a larger network. This network includes the anatomical structures used for the processing of the correct condition.

4. Experimental procedures

4.1. Participants

Eighteen (10 females) healthy adults (age 18–31 years, mean 25 years) volunteered as participants. All subjects were right handed as measured by the Edinburgh Handedness Inventory (Oldfield, 1971). Seventeen scored with 100 indicating strong right-handedness. The one exception scored with 47. All had no known hearing deficit and were native speakers of German.

4.2. Materials

Experimental design and most of the sentence material were taken from a previous study of Friederici et al. (2000). The material consisted of 130 correct and 130 semantically incorrect sentences (for an example, see Table 3). The critical word rendering the sentence correct or incorrect always appeared at the end of the sentence. Note that the penultimate word (German: 'wurde') was identical in all sentences in order to avoid a potential confound for the analysis of the final word. Additionally, there were 260 filler sentences. Half of the fillers were correct sentences and the other half had a syntactic error. This part was not analyzed here as it was described previously (Friederici et al., 2000). Subjects' individual hearing thresholds were determined for each ear separately and stimuli were presented 48 dB above.

4.3. Procedure

Subjects were required to listen to sentences presented auditorily as connected speech and to judge their correctness

after each sentence. A delayed response was introduced to minimize a possible contamination by the motor preparation processes. The response was triggered by a cue, which was displayed on the screen 1000 ms after the offset of the sentence final word and happened on average 1674 ms after the onset of that word. The cue contained a happy and a sad symbolic face (smiley) presented at either side of the screen and subjects were asked to answer with the thumb, which corresponded to the side of the happy face for the correct sentences or to the side of the sad face for the incorrect ones. The arrangement of both faces at the screen was counter-balanced over all stimuli. All sentences were spoken by a trained female native speaker of German. They were recorded on digital audiotape and later down sampled to 22.05 kHz with a 16-bit resolution. In order to guarantee precise time locking of the MEG signal to the onset of the critical word, target words in each sentence were marked by means of separate triggers.

To further increase the signal-to-noise ratio of the sentences, subjects participated in two sessions separated by at least 1 month. In each session, the complete stimulus set was presented resulting in a total of 260 sentences per condition and subject.

4.4. Data recordings

The MEG was recorded in a magnetically shielded room (Vacuumschmelze, Hanau) with a whole-head magnetometer (Magnes WHS 2500, 4D-Neuroimaging, San Diego, CA, USA) while subjects were listening to the auditory stimuli. One hundred forty-eight channels of MEG, together with 4 electrodes of electrooculogram (EOG) and trigger markers, were recorded continuously. Across the two recording sessions, the head position of a subject was kept constant by bringing the MEG chair into the same position. Within one session, the head position of subjects was determined via five head-mounted coils, which were sequentially activated and localized before and after each of the recording blocks. These data were used for a transformation into an average sensor system and rejection of excessive movements during a session (see below). Triggers were added on-line at the beginning of each sentence. Additional triggers were inserted off-line to the onset of each word. The MEG signal was on-line band-pass filtered (0.1–100 Hz) and sampled at a rate of 508.63 Hz. Data were recorded in four separate blocks per session. Block length was about 12 min. Subjects were asked not to move during a block. Before and after each experimental block, the position of the sensor array with respect to the nasion-ear coordinate system was measured via the abovementioned head coils. Blocks during which subjects' head had moved for more than 8 mm were discarded from further analysis.

4.5. Data preprocessing

First, the artifact suppression technique suggested by Robinson (1989) was applied to minimize the influence of environmental disturbances to the MEG data. Second, the MEG signals were filtered off-line (0.5–8 Hz, 4561 points FIR, hamming window) to improve the signal quality while keeping the broad N400 deflection untouched. The filter was specifically designed for a strong DC suppression (>100

dB at DC, >75 dB up to 0.2 Hz) to replace the baseline correction. In addition, we wanted to maximize the signal-to-noise-ratio, which is necessary for optimal source localization. The N400 component corresponds to a frequency of about 6 Hz, one of the strongest distortions is caused by α -activity. Thus, we selected a low-pass filter with an upper 3-dB edge frequency of 8 Hz. Epochs were selected as 1100-ms range (from –100 to 1000 ms with respect to the onset of the critical word). Prior to further analysis, epochs were screened for eye movements and other artifacts. Epochs were excluded from any further analysis if (a) the standard deviation of the EOG within a sliding 200-ms time window exceeded 30 μ V for the horizontal EOG and 50 μ V for the vertical EOG; (b) the standard deviation of any MEG recording channel within a sliding 200-ms time window exceeded 1100 fT; or (c) the drift of the MEG recording within the epoch was larger than 3000 fT. In addition, bad channels were rejected based on the cross-correlation coefficients between adjacent channels. A channel is classified as non-operational if the median of correlation coefficients to its immediate neighbors is less than 0.72. This method is motivated by the smoothness of magnetic fields. An electrically active brain region is producing a smooth magnetic field. The superposition of all of them is detected by the MEG sensors. Because of the smoothness, signals of neighboring channels are highly correlated with each other. A channel that does not reach a minimum median correlation to its immediate neighbors can therefore be considered as non-operational.

Finally, epochs were averaged for correct and semantically incorrect final words and for each experimental block separately, that is, 0 ms corresponds to the onset of the final word. Mean MEG sensor position across all measurement blocks of both sessions was estimated. Magnetic data of single blocks were transformed to the mean position by a model-based interpolation scheme (Knösche, 2002) and averaged thereafter. These averages were subjected to the final localization step.

4.6. Source localization

Source localization was performed using individually scaled versions of a standardized brain as so-called volume conductors (Maess et al., 2002). For this purpose, the skin surface of the standard model was fitted to the digitized shape of the subjects head by estimating five scaling factors. Thereafter, an individual reconstruction surface (so-called source space) was created at a depth of 1 cm below the inner skull surface. As a result, the position of source space is approximating the position of cortical tissue of each individual. The reconstruction surface was meshed with 1222 nodes. Current density estimates were computed using the minimum-norm least squares method (MNLS; also referred to as L2-norm) for each condition and subject using lead field normalization (Fuchs et al., 1999; Hämäläinen and Ilmoniemi, 1994). For our localization, we used the software package ASA (<http://www.ant-software.nl>) in combination with a library of routines (Inverse Toolbox) available from the SIMBIO project (<http://www.simbio.de>). In ASA, we chose Tikhonov regularization, where the regularization value was set to 20%, which is an approximation of the

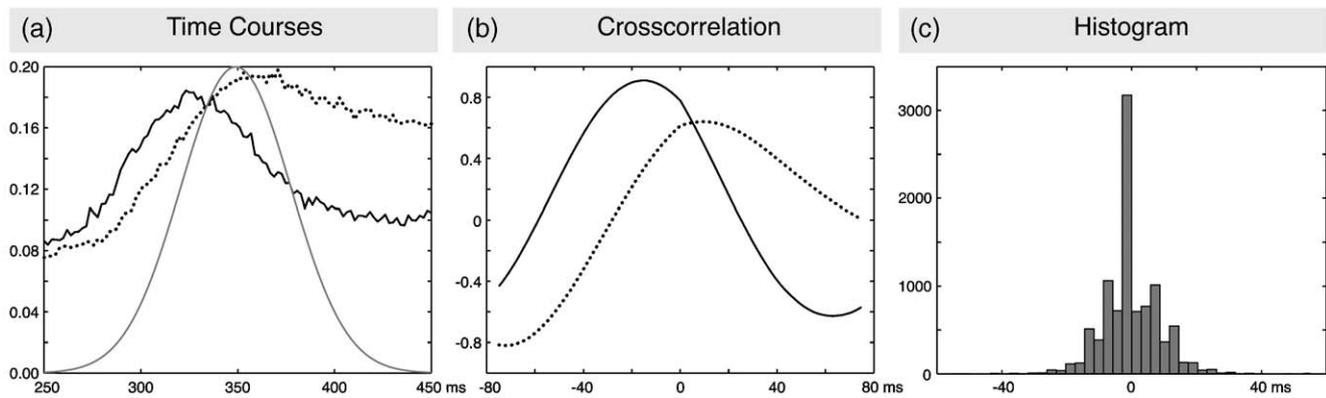


Fig. 3 – This set of figures displays (a) time courses of the correct (solid), the semantically incorrect (dotted), and test function (gray) within the TW 250–450 ms; (b) the cross-correlation functions between the test and correct (solid) or incorrect (dotted) for different time lags (x -axis). The difference between the displayed maxima of both curves is taken as latency difference between the original signals shown in panel a. Panel c provides the histogram of all bootstrapped latency differences estimated from 10,000 samples. For region LSTG, the latency difference was -26 ms, which means that the maximal deflection is reached 26 ms earlier in the correct condition. The histogram represents a distribution which has a mean of 0.0 ms and a standard deviation of 8.3 ms. Only 0.5% of the constructed samples had the same or even larger lead for the correct condition.

inverse of the signal-to-noise ratio (Knösche, 1997). The value was estimated experimentally: Larger values resulted in spatially simpler but similar solutions, smaller values resulted in spatially more complex and different solutions. Twenty percent was estimated as the smallest regularization value still yielding stable solutions. Additionally, two further iteration steps were computed to get spatially more focal BSCD distributions (Gorodnitsky et al., 1995). During each iteration, the last solution is taken as a weighting matrix for the next, thereby sharpening the very distributed L2-Norm. Two iterations were chosen as a compromise between distributed and single equivalent dipole-type solutions, which are reached with five and more iterations. In case of MEG data, the L2-minimum norm method determines the strength of two orthogonal tangential dipoles at each of the source space nodes. The third, the radial dipole component, cannot be determined with comparable accuracy and therefore was suppressed for the sake of stability. By this procedure, the measured field strength is mapped to a current distribution at the brain's surface. Nakamura et al. (2004) have shown via simulations that this method reproduces brain activity originating from the outer cortical mantle in a very reliable way. Depth information, however, is not provided.

Each individual source space was spatially normalized to the Talairach brain (Talairach and Tournoux, 1988). A further analysis of the current distribution needs the concept of restricted regions or regions of interest (ROI), which are co activated during the function under concern. ROIs were defined based on the group average of BSCDs in the following way: Starting from the dipole position, which scored highest at a latency between 300 and 550 ms in the mean BSCD map of the semantically incorrect condition, a maximum of ten neighboring positions following in strength were included if their score was higher than 70% of the maximal value and the spatial distance to the maximum was smaller than 18 mm.

Seven local maxima were found and consequently seven ROIs were defined. An eighth ROI was constructed as a homologue to the LIFG ROI resulting in same number of ROIs per hemisphere.

The mean magnitudes of BSCD were determined for each ROI. Paired t tests of these BSCD values were computed to compare the correct and semantically incorrect condition for two time windows 300–400 ms and 450–550 ms.

Latency differences between conditions (within each ROI) or between ROIs (within each condition) were estimated via cross correlating a test signal with the two signals under concern. A gaussian curve with a full width at half height (FWHH) of 80 ms was taken as test signal. Latencies of maximum cross correlation of each condition to the test signal were estimated and tested for significance between ROIs and conditions using a bootstrap procedure. A time window 250–450 ms was taken to determine activity onsets within the abovementioned TW 300–400 ms. Fig. 3 is provided as an example to illustrate how the latency difference estimation and their test for significance were done.

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